## REMARKS

With the present submission, claims 1, 16, 21, 42, 44 and 47 have been amended. Claims 2, 4-12, 22-29, and 32-35 were previously canceled without prejudice or disclaimer. Accordingly claims 1, 3, 13-21, 30-31, and 36-47 are currently under consideration. Claims 1, 3, 13-21, 30, 31, and 36-47 are rejected. Applicants respectfully request reconsideration of the application, withdrawal of all rejections, and allowance of the application in view of the amendments and remarks below.

### The Invention

The present invention provides novel compositions in the field of RNAi and methods for using such compositions in modulating NOGO receptor gene expression. These compositions are extensively and differentially modified double stranded nucleic acids ("dsNAs") of defined length and complementarity. In particular, extensively modified refers to either the percentage of modifications in each composition overall and/or to the unique combination of nucleotide modifications in each composition. The compositions of the invention have differential modification patterns. In certain embodiments, these differential modifications patterns are between purine and pyrimidine nucleotides. These dsNAs are useful in mediating RNA interference against NOGO receptor gene targets.

### Amendments to the Specification

Applicants have amended the specification to include corrected priority information as requested by the Office. The amendment does not add any new matter. It is respectfully requested that the amended priority be incorporated into the application.

### Amendments to the Claims

Claim 1 has been amended to merely eliminate the word "about." Claims 21, 42, 44 and 47 have also been amended. These amendments are fully supported by the application as filed. No new matter has been added. To expedite prosecution and in compliance with the Office's request (*see* Office Action at 3), representative support from the instant application and various priority applications for all claims currently pending is provided in the following table.

| Claim No. | Support from U.S. Appl. No. 10/576,690 | Support from PCT/US03/05028 | Support from U.S. Appl. No. 60,363,124 |
|---|---|---|---|
| 1 | 8:18-32, 9:7-17, 10:1-12, 10:22-28, 12:1-4, 12:15-16, 13:9-12, 13:18-20, 14:8-11, 16:4-10, 16:18-32, 27:22-30, 28:3-6, 29:19-28, 30:9-19, 33:4-34:4, Tables I-IV, Figs. 4-5 | 8:15-19, 8:21-30, 9:1-5, 9:6-13, 9:20-26, 10:4-11, 10:13-15, 12:13-15, 13:3-6, 14:3-10, 14:19-24, 16:26-17:27, 23:15-20, 28:3-23, 29:3-20, 29:28-30:10, Tables I, IV and V, Fig. 18 | 3:15-17, 5:14-17, 10:3-11:25, 12:4-9, 18:1-5, 19:11-14, 24:15-22, 35:29-30, Tables I & III |
| 3 | 16:3-7, 17:6-7, 31:11-14, Figs. 4-5 | 8:21-22, 30:2-4, Tables I and IV, Fig. 18 | 35:29-31, Table I |
| 13 | 21:10-12, 33:4-34:3, 37:20-25 | 16:26-17:26, 22:10-15, 22:27-23:2 | 6:19-7:11, 10:3-11, 17-25 |
| 14 | 33:4-34:3, 46:14-17, 46:23-26, 49:1-4 | 16:26-17:26, 27:28-28:2 | 6:19-7:11, 5:14-17, 10:3-11, 17-25 |
| 15 | 21:10-17, 22:8-10, 33:4-34:3, 37:20-25, 46:9-14, 46:18-23, 46:30-47:4, 47:8-13 | 16:27-17:26, 22:10-12, 27:23-28 | 6:19-7:11, 10:1-30 |
| 16 | 21:27-30, 28:20-23, 37:14-15, 37:24-25, 49:11-14, 120:17-28 | 20:30-31, 21:16-17, 22;2-3, 68:17-18 | 10:3-11, 10:17-25 |
| 17 | 21:23-30, 28:20-23, 120:13-28 | 10:19-20, 29:13-14, 31:14-16, 86:16-31 | 8:21-25, 13:18-14:9 |
| 18 | 33:4-34:3, 47:19-24, 47:28-48:2, 48:8-13, 48:17-22, 49:4-8 | 16:26-17:26, 28:3-9, 28:13-19, 28:24-30 | 6:19-7:11, 10:3-16,10:25-30 10:31-11:25 |
| 19 | 33:4-34:3, 47:24-27, 28:2-5, 49:8-11, | 16:26-17:26, 35:15-18 | 6:19-7:11, 10:31-11:25 |
| 20 | 28:13-16, 33:4-34:3, 48:13-16, 54:24-27 | 16:26-17:26, 28:30-29:2, 35:32-36:3, | 6:19-7:11, 10:31-11:25 |
| 21 | 23:18-20, 28:23-26, 31:6-8, 35:21-36:14 | 10:30-11:2, 15:3-4, 19:11-20:2, 29:23-27 | 8:26-9:13, 9:23-25 |
| 30 | 24:28-20, 27:1-3, 28:26-27, 29:19-28, 35:21-36:4 | 11:20-21, 19:11-20:2 | 8:26-9:13 |

| Claim No. | Support from U.S. Appl. No. 10/576,690 | Support from PCT/US03/05028 | Support from U.S. Appl. No. 60,363,124 |
|---|---|---|---|
| 31 | 30:20-21, 65:16-21 | 45:4-9, 90:12-44 | 45:32-46:13 |
| 36 | 33:4-34:3, 47:4-7, 47:13-18, 49:20-32 | 16:26-17:26 | 6:19-7:11, 10:3-11, 10:17-25 |
| 37 | 15:24-28 | 13:11-14, 19:24-25, 23:24-25, 29:23-26, 69:15-20 | 4:9-11, 9:7-10, 12:4-13 |
| 38 | 16:7-11, 21:20-22, 23:22-24, 31:11-17 | 14:6-10, 66:28-30, | 5:13-17, Table I |
| 39 | 31:29-32:21, 36:15-37:7 | 20:3-25 | 9:14-10:2, 11:6-11 |
| 40 | 41:30-42:6, 50:16-26 | 31:28-32:6 | |
| 41 | 50:1-10, 50:25-26, 54:27-31, 117:22-26, Table IV | 31:28-32:6, 36:17-20, 83:26-30 | 37:28-31 |
| 42 | 8:18-32, 9:7-17, 10:1-12, 10:22-28, 12:1-4, 12:15-16, 13:9-12, 13:18-20, 14:8-11, 16:4-10, 21:27-30, 27:22-30, 28:3-6, 28:20-23, 29:19-28, 30:9-19, 33:4-34:4, 37:14-15, 37:24-25, 49:11-14, 120:17-28, Tables I-IV, Figs. 4-5 | 8:15-19, 8:21-30, 9:1-5, 9:6-13, 9:20-26, 10:4-11, 10:13-15, 12:13-15, 13:3-6, 14:3-10, 16:26-17:27, 20:30-31, 21:15-17, 22:2-3, 23:15-20, 28:3-23, 29:3-20, 29:28-30:10, 68:16-18, Table V, Fig. 18 | 3:15-17, 5:14-17, 6:19-7:12, 10:3-11:25, 12:4-9, 18:1-5, 19:11-14, 24:15-22, 35:29-30; Tables I & III |
| 43 | 30:20-21, 65:16-21 | 45:4-9, 90:12-14 | 45:32-46:13 |
| 44 | 8:18-32, 9:7-17, 10:1-12, 10:22-28, 12:1-4, 12:15-16, 13:9-12, 13:18-20, 14:8-11, 16:4-10, 16:18-32, 27:22-30, 28:3-6, 29:19-28, 30:9-19, 33:4-34:4, Tables I-IV, Figs. 4-5 | 8:15-19, 8:21-30, 9:1-5, 9:6-13, 9:20-26, 10:4-11, 10:13-15, 12:13-15, 13:3-6, 14:3-10, 14:19-24, 16:26-17:27, 23:15-20, 28:3-23, 29:3-20, 29:28-30:10, Table V, Fig. 18 | 3:15-17, 5:14-17, 6:19-7:12, 10:3-11:25, 12:4-9, 18:1-5, 19:11-14, 24:15-22, 35:29-30, 42:4-16, Tables I & III |
| 45 | 30:20-21, 65:16-21 | 45:4-9, 90:12-14 | 45:32-46:13 |
| 46 | 55:28-57:6 | 37:21-38:15 | 15:10-26 |

| Claim No. | Support from U.S. Appl. No. 10/576,690 | Support from PCT/US03/05028 | Support from U.S. Appl. No. 60,363,124 |
|---|---|---|---|
| 47 | 55:28-57:6 | 27:21-38:15 | 15:10-26 |

Again, the citations provided are merely illustrative and not intended to be comprehensive. Additional support for these claims can be found elsewhere throughout the applications.

Amendments to and cancellations of the claims are made without prejudice or disclaimer and do not constitute amendments to overcome any prior art or other statutory rejections. They are fully supported by the specification as filed as well as various priority applications, as explained above, and thus do not introduce new matter. Additionally, these amendments and cancellations are not and should not be construed as admissions regarding the patentability of the claimed subject matter. Applicants reserve the right to pursue the subject matter of previously presented claims in this or in other appropriate patent applications. Accordingly, Applicants respectfully request the entry of the amendments presented herein.

**Priority**

The Office asserts that the effective priority date of the instant claims is August 20, 2004, which is the filing date of priority document PCT/US04/26930. Office Action at 4. According to the Office, support for the invention as now claimed cannot be found in other parent applications. *Id.* Specifically, the Office alleged that support for a chemically modified nucleic acid molecule wherein about 50 to 100 percent, or alternatively, at least 50 percent, of the nucleotides are modified with modifications independently selected from 2'-O-methyl, 2'deoxy-2'-fluoro, 2'-deoxy, phosphorothioate, and deoxyabasic modifications cannot be found. *Id.* at 4-5

Applicants respectfully disagree and submit that the instant claims are entitled to an earlier priority date of March 11, 2002, based on U.S. Provisional Application 60/363,124. In compliance with the Office's request that Applicant point with particularity to where the support can be found in the specification of the prior applications, the Office is directed to, for example, PCT/US03/05028, filed on February 20, 2003, where support can be found *inter alia,* at 8:15-19, 8:21-30, 9:1-5, 9:6-13, 9:20-26, 10:4-11, 10:13-15, 12:13-15, 13:3-6, 14:3-10, 14:19-24, 16:26-17:27, 23:15-20, 28:3-23, 29:3-20, 29:28-30:10, Tables I, IV and V, and Fig. 18. Likewise, the Office is directed to U.S. Application. No. 60/363,124, filed on March 11, 2002, where support

can be found *inter alia,* at 3:15-17, 5:14-17, 10:3-11:25, 12:4-9, 18:1-5, 19:11-14, 24:15-22, 35:29-30, and Tables I & III.

Claims are entitled to the filing date of the parent application under 35 USC §120, if the parent application complies with 35 USC §112, as to the subject matter of the current pending claims. See *In re Wertheim*, 541 F.2d 257, 261 (CCPA 1976). "[T]he invention claimed does not have to be described *in ipsis verbis* in order to satisfy the description requirement of §112." *Id.* at 265 (quoting *In Re Lukach* 442 F.2d 967, 969 (CCPA 1971). The instant claims are fully supported by the priority documents, as discussed *supra*. Thus, Applicants respectfully request that the Office accord the application its rightful priority date of March 11, 2002.

**Double Patenting Rejections**

**Statutory Type Double Patenting**

Claims 1, 3, 13-21, 30, 31, 36-41, and 46 were provisionally rejected under 35 USC 101 as allegedly claiming the same invention as that of claims 1, 3, 14-21, 30, and 35-39 of co-pending Application No. US Publication 20050182008. Applicants submit that Application No. US Publication 20050182008 lapsed on January 31, 2008, thus rendering the rejections moot. Accordingly, Applicants respectfully requests withdrawal of the statutory double patenting rejections.

**Obviousness-Type Double Patenting**

Claims 42-45 and 47 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being obvious over claims 1, 3, 14-21, 30, and 35-39 of co-pending Application No. US Publication 20050182008. Applicants submit that Application No. US Publication 20050182008 lapsed on January 31, 2008, thus rendering the rejections moot. Accordingly, Applicants respectfully requests withdrawal of the obviousness-type double patenting rejections.

**Rejections under 35 U.S.C. § 112, First Paragraph**

Claims 46 and 47 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to meet the enablement requirement. Applicants respectfully traverse the rejections.

Specifically, the Office alleged that while the claims are enabled for a method of modulating the expression of human NOGO receptor gene in a cell *in vitro*, they are not enabled for modulating the expression of human NOGO receptor gene in a cell *in vivo*. Office Action at pages 7-8. The Office alleged that as there are no examples in the specification of delivery of modified nucleic acid complementary to the NOGO receptor to cells *in vivo* or modulation of expression of the NOGO receptor *in vivo* and in view of the unpredictability of the art, as purported supported by Lu *et al.* ((2005) in RNA Interference Technology (Cambridge, Appasani, ed.)), Samarsky *et al.* ( RNA Interference Technology (2005) pages 389-394) and Paroo *et al.* ( Trends I Biotechnology 2004 Vol. 22:390-394), the scope of claims are not enabled, as undue experimentation would be required to practice the invention *in vivo*. *Id.* at 9-14. Applicants respectfully submit that the Office's reliance on the cited references are insufficient evidence to establish lack of enablement.

"[E]nablement requires that the specification teach those in the art to make and use the invention without 'undue experimentation.' That some experimentation may be required is not fatal; the issue is whether the amount of experimentation required is 'undue.'" *In re Vaeck*, 947 F.2d 488, 495 (Fed. Cir. 1991)(citation omitted, emphasis in original). "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighting many factual considerations." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). "[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of first paragraph of § 112 unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *In re Marzocchi*, 439 F.2d 200, 223 (CCPA 1971) (emphasis in original).

The specification provides extensive guidance and teachings of a method of modulating the expression of the human NOGO receptor gene in a cell using a chemically modified nucleic acid of the invention. Specifically, the specification teaches various methods for modulating NOGO gene expression, including down-regulating NOGO gene expression, at pages 49-61, and teaches how to treat various neurological diseases, such as, for example, Alzheimer's, dementia, multiple sclerosis, etc., using the double stranded nucleic acid molecules at pages 61-62, 140-

141, and 155-156. Moreover, the specification provides various methods for administering the double stranded nucleic acid molecules *in vivo* and animal models for use *in vivo* (pages 124-139, 153-154). The specification also provides dosages and formulations (pages 131-135) and a method for testing for *in vivo* RNAi activity (Example 7). Thus, there is significant guidance provided by the specification on how to practice the claimed methods. This disclosure must be relied on for enabling support unless there is a reason to doubt the truth of these statements.

The Office has put forth no argument or evidence to contradict the veracity of these disclosures. "[I]t is incumbent upon the Patent Office, wherever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *In re Marzocchi*, 439 F.2d at 224. *See also, In re Wright*, 999 F.2d 1557, 1561-62 (Fed. Cir. 1993).

Rather than address the veracity of the statements in the specification, the Office instead relied on three references, Lu, Samarsky, and Paroo, as alleged evidence of unpredictability in the art of *in vivo* applications. These references do not provide, however, evidence of non-enablement, because the problems addressed in those references concerned optimized delivery for the clinical success and commercial viability of RNAi therapeutics in general. This is evidenced by specific language in the references and taking all the information of the references in context. For example, Lu is directed to "optimized local and system delivery of siRNA *in vivo*." Lu *et al.* ((2005) in RNA Interference Technology (Cambridge, Appasani, ed.)) at 303 (emphasis added). Further, although not discussed in the Office Action, Lu, in fact, discusses numerous successful *in vivo* applications that have been done, including his own work in 2002. *Id.* at 305-311. Lu states that the challenge for use as a commercial therapeutic is optimizing the delivery in terms of "pharmacokinetics and tissue distribution." *Id.* at 314. Likewise, Samarsky is directed to the "efficient delivery of RNA triggers to target tissue" and discusses the cost and financial resources required to effect efficient delivery. Samarsky *et al.* ( RNA Interference Technology (2005) at pages 384 and 394 (emphasis added). Samarsky explicitly states that "RNAi is a powerful target discovery and validation tool that may be applied to *in vitro* and *in vivo* models of disease" and even goes on to discuss a number of *in vivo* applications, some as early as 2000. *Id.* at 385 and 389-390. Similarly, Paroo discusses barriers to "widespread

applications" in terms of "the most effective delivery" and notes that the "most effective siRNA as identified in cell culture might not be optimal for use *in vivo*." Paroo *et al.* (Trends in Biotechnology 2004 Vol. 22, abstract and page 393) (emphasis added). Paroo, like Lu and Samarsky, also goes on to discuss examples of successful *in vivo* applications of siRNA. (*Id.* at 391).

The Office appears to suggest that the conditions for optimal delivery and the precise pharmacokinetics of the siRNA must be determined before the claims are enabled. However, the claims merely require that the expression of human NOGO receptor gene in a cell is modulated. The claims do not recite, nor should they be interpreted to require, the most effective or optimal modulation. Such considerations, *e.g.*, the most effective, optimized, or efficient delivery, go beyond what is required by the pending claims and also go beyond what is required for enablement under 35 USC 112 per se. It is well established that a therapeutic method need not be ready for clinical application in order to be enabled. *See In re Brana,* 51 F.3d 1560, 1567 (Fed. Cir. 1995); *see also FMT, Inc. v Yieldup Int'l Corp.,* 349 F.3d 1333, 1338 (Fed. Cir. 2003) ("Enablement does not require an inventor to meet lofty standards for success in the commercial marketplace. Title 35 does not require that a patent disclosure enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect.") Likewise, the Board of Patent Appeals and Interferences ("BPAI") has repeatedly noted that this is an improper standard for enablement. *See Ex Parte Rollins,* Appeal No. 2001-0869, page 8 (July 9, 2003) (unpublished) ("[E]vidence that a claimed method was not ready for clinical application is not enough to show nonenablement"); *see also Ex Parte Zavada*, Appeal No. 2001-1970, page 10, (July 23, 2003) ("[A] therapeutic method need not be ready for clinical application in order to be enabled . . . [u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development.").

Not only does the specification provide guidance and teachings on how to apply the methods for the expression of the human NOGO receptor gene in a cell, including teaching *in vivo* applications, such methods and others were well known in the art, as evidenced by the references cited by the Office and also standard manuals at the time. (*See, e.g.,* Molecular Cloning: A Laboratory Manuel (3-Volume Set) 3rd edition by Joseph Sambrook and David W.

Russel; Publisher: Cold Spring Harbor Laboratory Pr. (2000)). The Office has provided no fact based explanation focused on the claimed methods, *e.g.,* methods to modulate NOGO gene expression in a cell, as opposed to RNAi therapy as a general field, to contradict these teachings and to establish that the instant claims are non-enabled. Additionally, the Office has not demonstrated that using a double stranded nucleic acid molecule to target NOGO receptor would be inactive or otherwise fail to modulate NOGO receptor gene expression *in vivo*. For all of the reasons discussed, the Office has failed to demonstrate that that claims are not enabled across the full scope of the claimed subject matter and thus the Offfice has failed to meet its burden of establishing a *prima facie* case of lack of enablement.

To the extent that the Office alleges that trial and error experimentation would be necessary to practice the invention, Applicants point out, as was discussed *supra*, that a considerable amount of experimentation is permissible, if it is merely routine. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Moreover, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104 (Fed Cir. 1985); MPEP 7th ed., rev. 2 § 2164.01 (citing *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983); *see also In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995). Using the methods known in the art and described in the instant application, a skilled artisan could easily formulate and test double stranded nucleic acids *in vitro* and *in vivo* as a matter of routine experimentation. The fact that modified double stranded nucleic acids are being tested in clinical trials is further evidence that the amount of experimentation necessary to practice the invention is not undue.

For all of the reasons discussed above, the specification teaches one skilled in the art how to make and use the claimed invention. Accordingly, Applicants respectfully request withdrawal of the lack of enablement rejection under 35 U.S.C. § 112, first paragraph.

**Rejections under 35 U.S.C. § 103(a)**

Claims 1, 3, 13-21, 30, 31, and 36-47 were rejected under 35 U.S.C. § 103(a) as allegedly obvious in view of GenBank Accession Number NM_023004 (2003), in view of Groutsi *et al.* (Society of Neuroscience Abstracts, 2001 Vol. 27, No. 1 page 917), Hammond *et al.* (Nature

Genetics 2001, Vol. 2:110-119), Elbashir *et al.* (EMBO Journal 2001 Vol. 20:6877-6888), Matulic-Adamic *et al.* (US Patent No. 5,998,203) and Parrish *et al.* (Molecular Cell, 2000 Vol. 6:1007-1087). Applicants respectfully traverse for the reasons stated below.

The Office characterized the instantly claimed invention into elements, allegedly found each of the "characterized" invention elements in the cited references and alleged the invention was obvious based on the combination of the elements.

According to the Office, as the "GenBank Accession Number NM_023004 taught the sequence of the human NOGO receptor" and Groutsi taught "antisense RNA to the NOGO receptor for promoting spinal cord regeneration," one would be motivated to substitute the antisense RNA taught by Groutsi with chemically modified nucleic acids, as Hammond allegedly "taught that RNA interference is superior to antisense." Office Action at 17, 21 and 23.

While the Office admitted that neither the GenBank Accession Number NM_023004 nor Groutsi et al. "teach a chemically modified nucleic acid molecule comprising a sense strand and an antisense strand wherein the antisense strand is complementary to a human NOGO receptor RNA comprising SEQ ID No:325, wherein each strand is 18 to 27 nucleotides in length, wherein about 50 to 100% or at least 50% of the nucleotides in each of the sense and antisense strand of the chemically modified double stranded nucleic acid molecule are modified with modifications selected from 2'-O-methyl, 2'-dexoy-2'-fluoro, 2'-deoxy, phosphorothioate and deoxyabasic modifications," according to the Office, incorporation of these modifications would be obvious as "[i]t was well known in the art at the time of filing to incorporate one or more modifications . . . into oligonucleotides." (*Id.* at 117-18, and 22). The Office cited to Elbashir, Matulic-Adamic, and Parrish for support. *Id.* The Office then asserted that "one of skill in the art would be motivated to test various modifications . . . to stabilize and optimize delivery of the nucleic acid' and "to incorporate chemical modifications to about 50% to 100% . . . to test the overall effect on RNAi activity as taught by Elbashir *et al.*" Id. at 22-23. Additionally, the Office asserted that "[t]here would be a reasonable expectation of success" because "the chemistry was well known" and "merely selecting combinations of such modifications is considered a design choice." *Id.* at 23. Finally, according to the Office, "substituting the antisense RNA complementary to NOGO receptor taught by Groutsi *et al.* with a chemically modified nucleic acid molecule" would have

been successful as they are "functionally equivalent" and "substitution of one known element for another would have yielded predictable results." *Id.* at 23 -24. Applicants respectfully traverse.

First, it is noted that the Office's characterization of the instant invention lacks specific limitations, as set forth in claims 1 and 44, and thus is incomplete and inaccurate. Specifically, the Office fails to recognize the following elements of claim 1: i) a sense strand that is complementary to the antisense strand, and comprises an 18-27 nucleotide sequence of the human NOGO receptor RNA sequence (element d) and ii) that the molecules of the invention have differential modification patterns, *e.g.,* at least one 2'-O-methyl purine and one 2'-deoxy-2'-fluoro-pyrimidine nucleotide (element f). Likewise, the Office failed to recognize similar limitations with regard to the sense stand and the specific requirements of claim 44.

Second, it is submitted that the Office's description of at least some of the cited references is incomplete or inaccurate. Specifically, certain features of these references that have importance in the obviousness inquiry are missing. The Office reads Elbashir as "teaching modification of the internal nucleotides with 2'-deoxy or 2'-O-methyl modifications . . . [including ] complete substitution of one or both siRNA strands" *See Id.* at page 18. Although the Office notes that complete substitution abolished RNAi activity, the Office neglected to mention the express teaching in Elbashir that "[m]ore extensive 2'-deoxy [aside from substitutions of the 2 nt 3'-overhanging ribonucleotides] or 2'-O-methyl modifications reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNP assembly." *See* Elbashir, at page 6885, left column. Therefore, Elbashir teaches away from not just 100 percent modification of one or both strands with 2'-deoxy or 2'-O-methyl modifications, but also teaches away from any modifications beyond incorporation of up to four 2'-deoxy modifications at the 3'-end of each strand in a 42 nt duplex.

Additionally, it is further submitted that the Office's summary of Parrish is incomplete as well. For example, Parrish allegedly teaches "chemically synthesized double stranded siRNA molecules comprising various modifications in the sense or antisense strand, including 2'-deoxy-2'-fluoro modifications. . . . . One or both strands comprise modifications." Office Action at 20. Applicants respectfully submit that Parrish describes 2'-deoxy-2'-fluoro uridine modifications but not 2'deoxy-2'-cytidine modifications and further teaches that 2'-deoxy modification of cytidine is detrimental to RNAi activity. *See* Parrish, at page 1081, right column ("Modification of

cytidine to deoxycytidine … on either the sense or the antisense strand of the trigger was sufficient to produce a substantial decrease in interference activity."). Furthermore, while Parrish described 2'-deoxy-2'-fluoro modification of uridine in either the sense strand or the antisense strand, there is no description of this modification simultaneously in both strands, as was first taught by Applicants. *See, e.g.,* Parrish, at page 1081, left column, Figure 5B (describing that interference activities of unc-22 were retained with a 2'-uracil → 2'-fluorouracil in the sense strand and unmodified RNA antisense strand; or with an unmodified RNA sense strand and a modified uracil → 2'-fluoro uracil antisense strand). Parrish does not teach 2'-fluoro modification of cytidines at all. Parrish does not teach 2'-O-methyl modifications. Also, Parrish does not teach double stranded nucleic acids with one or more pyrimidines differentially modified from one or more purines, a claim limitation of the instant invention and first taught by Applicants. Finally, Parrish repeatedly noted that activity was more sensitive to modification of the antisense strand than of the sense strand and that, depending on the type of modification and location, inactivity could result (*see e.g., id.* at pages 1081, 1082 and 1084), thus confirming that use of "known modifications" from the antisense and ribozyme art had unpredictable results with respect to RNAi activity prior to the teachings of the instant application.

Even disregarding these inaccuracies, the cited references, alone or in combination, do not teach or suggest a nucleic acid duplex having separate strands of 18-27 nucleotides with 50 to 100 percent modifications on each strand. Groutsi teaches antisense molecules, which are single stranded, and does not teach modifications. GenBank Accession Number NM_023004 (2003) is single stranded. Matulic-Adamic teaches ribozymes that are substantially single-stranded, which require at least one stem-loop structure for activity, and which consequently do not have two separate strands. Additionally, Matulic-Adamic does not contemplate siRNA or RNA interference, and certainly does not contemplate differential modification strategies. Hence, none of these references teach separate strands with 50 to 100 percent modifications on each strand or differential modification. Likewise, Hammond, Elbashir, and Parrish, individually or in combination, do not cure this deficiency. Hammond does not disclose or teach modifications. Elbashir teaches away from any modification beyond the four 3'- terminal residues on each strand of a 42 nt duplex. Parrish does not teach chemical modification of short nucleic acid duplexes and fails to teach simultaneous modification of both strands of the duplex.

Moreover, none of the references teach individually or collectively a double stranded nucleic acid that has one or more 2'-O-methyl purines and one or more 2'-deoxy-2'-fluoro pyrimidines, much less this feature in combination with 50 to 100 percent modifications to each strand.

Subsequent to the decision in *KSR Int'l Co. v. Teleflex Inc.,* 127 S.Ct. 1727 (2007), the Board of Patent Appeals and Interferences ("BPAI") has continued to recognize the criticality of a finding of all the limitations in a claim to establish a *prima facie* case of obviousness. According to the BPAI:

> [A]n examiner must make "a searching comparison of the claimed invention – *including all its limitations* - with the teaching of the prior art." *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995) (emphasis added). Thus, "obviousness requires a suggestion of all limitations in a claim." *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d, 1333, 1342 (Fed. Cir. 2003) (citing *In re Royka*, 490 F.2d 981, 985 (CCPA 1974)).

*Ex Parte* Wada, BPAI, Appeal 2007-377, page 7 (Jan. 15, 2008) (unpublished). *See also, Ex parte* Shepard, BPAI, Appeal 2008-0401, page 7 (Jan. 3, 2008)(unpublished) (BPAI reversed the Examiner's rejection of obviousness, because "having failed to demonstrate that the references teach the limitations of claim 11, the Examiner failed to establish a *prima facie* case of obviousness for claims 17 or 18 which depend from claim 11.")

As discussed *supra*, the references cited do not teach or suggest a double stranded nucleic acid with separate strands having 18-27 nucleotides in each strand wherein i) 50 to 100 percent of the nucleotides in the sense strand and 50 to 100 percent of the nucleotides in the antisense strand are chemically modified with modifications independently selected from the group consisting of 2'-O-methyl, 2'-deoxy-2'-fluoro, 2'-deoxy, phosphorothioate and deoxyabasic modifications; and ii) one or more of the purine nucleotides present in one or both strands of the nucleic acid molecule are 2'-O-methyl purine nucleotides and one or more of the pyrimidine nucleotides present in one or both strands of the nucleic acid molecule are 2'-deoxy-2'-fluoro pyrimidine nucleotides. Thus, the cited documents, alone or in combination, fail to show or suggest all of the claim limitations. Accordingly, the Office has not put forth a *prima facie* case of obviousness.

Applicants note that the Office has attempted to completely circumvent the requirement of a finding or suggestion of all the limitations in the claims by amalgamating the specific enumerated features of different elements of the claims into a "design choice" descriptor, e.g.,

the requirement that 50 to 100 percent of each strand is modified with 2'-O-methyl, 2'-deoxy-2'-fluoro, 2'-deoxy, phosphorothioate and deoxyabasic modifications and the requirement that one or more of the purine nucleotides present in one or both strands of the nucleic acid molecule are 2'-O-methyl purine nucleotides and one or more of the pyrimidine nucleotides present in one or both strands of the nucleic acid molecule are 2'-deoxy-2'-fluoro pyrimidine nucleotides are described as design optimizations. These are structural features of the pending claims, not merely design optimizations. According to the CCPA, "[a]ll words in a claim must be considered in judging the patentability of the claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385 (CCPA 1970). *See also, Ex Parte* Scioscio, BPAI, Appeal 2007-2893, page 5 (Aug. 2, 2007). ("By failing to address all the claim limitations, the Office's *prima facie* case of obviousness is in error.")

Even assuming *arguendo* that there was a finding or suggestion of all the elements in the prior art, which is not the case, more is required to establish a *prima facie* case of unpatentability due to obviousness. Additionally, "*there must be some articulated reasoning* with some rational underpinning to support the legal conclusions of obviousness." *Id.* at 7 (quoting *KSR Int'l v. Teleflex Inc.,* 127 S. Ct. 1727, 1741 (2007)(quoting *In re Kahn,* 441 $.3d 977, 988 (Fed. Cir. 2006)(emphasis added))). The Supreme Court recognized that "inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known," (*KSR*, at 1741), and thus emphasized various factors to assess in determining obviousness. One factor particularly pertinent to the instant case and the references cited by the Office is whether, when purported known elements are combined, there is predictability of yielding the claimed results (*id.* at 1731).

The Office relied on arguments of mere "design choice," and alleged "routine nature of testing various chemical modifications" to support its position of obviousness. Office Action at 21- 22. However, this type of analysis does not meet the standard for determining obviousness. Specifically, the modifications recited in the present claims are not a peripheral issue of design choice, but rather required elements of the claims. To support an argument "that routine experimentation within the teachings of the art will defeat patentability requires a primary determination of whether or not [Applicants'] experimentation comes within the teachings of the

art. Whether the subsequent experimentation is termed "routine" or not is of no consequence." *Pfizer, Inc. v. Apotex, Inc.,* 480 F.3d 1348, 1367 (Fed. Cir. 2007) quoting *In re Fay*, 347 F.2d.597, 602 (C.C.P.A. 1965). For routine experimentation to support obviousness, the Court in *Pfizer* found that the prior art had to provide not only the means, but also had to predict the results, i.e., such that "there was a reasonable expectation of success at the time the invention was made, and [one] merely had to verify that expectation. *Id.* Applicants' experimentation does not come within the teachings of the art at the time the invention was made for the reasons discussed below.

At the time of filing of the present application, RNAi was still a new technology. The art cited by the Office and other art at the time, made it clear that modifications of dsRNA and siRNA molecules produced unpredictable results in terms of RNAi activity. *See e.g.,* discussion of Parrish and Elbashir, *supra*. Modifications were known to impact the structural characteristics of RNAi molecules and hence their activity in an unpredictable manner; this was in direct contrast to the antisense and ribozyme art at that time. Thus, reliance on the use of "known" chemical modifications in the ribozyme and antisense art, such as Matulic-Adamic, to guide the extent, location, and types of modifications to siRNA is misguided. Although antisense and ribozymes are all nucleic acid based technologies, they differ substantially from the present invention both mechanistically and structurally, particularly in relation to the chemical modification strategies that allow such molecules to remain active. Just as antisense modifications are not amenable to ribozyme technology and *vice versa*, neither of these nucleic acid technologies provides any insight or guidance into the extent and locations of chemical modification on siRNAs. Contrary to the Office's assertion, these nucleic acid molecules are not structural or functional equivalents. For example, critical to RNAi technology are dicer and RISC protein complex, neither of which is involved in antisense or ribozyme technology. Chemical modifications which prevent or affect dsRNA/siRNA interaction with either of these proteins abolishes or decreases RNAi activity. Thus, particularly with respect to the number and location of the chemical modifications, prior art teachings relating to chemical modification of antisense and ribozymes shed no light on whether the modification(s) will be tolerated by RNAi molecules. The data in the references cited and the knowledge of the mechanisms of these different classes of compounds bears this out. *See e.g.,* Parrish and Elbashir. Consequently,

based on the art at the time of the filing, i.e., before the Applicants' teaching, a skilled artisan would not have had a reasonable expectation of success in achieving compositions as presently claimed that had RNAi activity. Thus, according to current case law, the standard of obviousness has not been met.

The Office alleges "[t]here would be reasonable expectation of success to apply chemical modifications to about 50% to 100% . . .since Elbashir et al. taught the design of such nucleic acids was known to be successful in the art" As Elbashir was not successful in modulating RNAi expression with complete modifications on one or both strands, Applicants conclude that the Examiner seems be arguing that the predictability analysis is limited to the reliability of being able to synthesize the compound. However, this analysis is in error. The predictability analysis must also take into account whether the compound will work for its intended purpose, *i.e.,* solve the solution that was intended to be solved. *See Pfizer, Inc.,* 480 F.3d at 1364. (According to the court, predictability required a finding that "the skilled artisan would have had that reasonable expectation of success that an acid addition salt of besylate would form **and would work for its intended purpose"** (emphasis added)). In the instant case, the solution to be solved and the intended purpose of the invention is to modulate the NOGO receptor gene. Thus, the predictability of obtaining RNAi activity must be included in the analysis. Applicants respectfully request that the Office point to the specific teaching(s) in the cited references that demonstrate that one skilled in the art would have had a reasonable expectation that siRNA molecules having 50 to 100 percent chemically modified nucleotides in each strand and having one or more 2'-O-methyl purine nucleotides in one or both strands and one or more 2'-deoxy-2'-fluoro pyrimidine nucleotides in one or both strands of the nucleic acid molecule would retain RNAi activity.

Additionally, the Office has taken the surprising and highly unprecedented position that art which teaches away is actually motivating art and thus renders the invention obvious. According to the Office, even though Elbashir teaches that complete modification of one or both strands abolishes activity, one would have been motivated to incorporate 50-100 percent chemical modifications in both strands to determine "the tolerances of chemical modifications for RNAi activity." *Id.* at 23. Not only is this paradoxical, it is also contrary to federal case law and to the rules promulgated in the MPEP. The Supreme Court in KSR emphasized the key criticality of a teaching away reference, stating that, "[w]hen the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more

likely to be nonobvious." *KSR International. Co.* 127 S. Ct. 1727, 1740 (2007 (citing *United States v. Adams*, 383 U.S. 39, 51-52 (1966)). Proceeding when there is a teaching away supports nonobviousness, not motivation. *See also*, MPEP §2145 ("proceeding contrary to accepted wisdom is evidence of nonobviousness").

Elbashir expressly taught and warned against using more than two 2′-deoxy modified nucleotides at the 3′-ends or 2'-O-methyl modifications in a section of the article aptly entitled, "The siRNA user guide":

> . . .2′-deoxy substitution of the 2 nt 3′ overhanging ribonucleotides do not affect RNAi, but help to reduce the costs of RNA synthesis and may enhance RNAse resistance of siRNA duplexes. More extensive 2′-deoxy or 2′-O-methyl modifications, reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNP assembly.

Elbashir (EMBO), at page 6885, left column *(emphasis added)*. Elbashir also taught that complete modification of one or both strands with 2′-deoxy or 2′-O-methyl "abolishes" activity. *Id*. at 6881-6882. Despite this teaching, Applicants proceeded to make highly modified double stranded nucleic acid molecules for use in RNAi modulation even though the art taught against such modifications. This is strong evidence of nonobviousness.

Applicants note also that the Office disregards the teaching away by Elbashir by stating that :"[i]t is noted that complete substitution of one or both siRNA strands .. .. . abolished RNAi activity, however, the instant claims do not recite any functional language, therefore the skilled artisan would have been motivated to incorporate extensive substitutions/chemical modification to a siRNA to determine overall RNAi activity" *Id*. at 19. It appears that the Office is implying that Elbashir's teachings regarding modifications that abolish activity would have no impact on the motivation to make the claimed molecules. First, Applicants note that some of the rejected claims are method claims, which do have a limitation that modulation of the NOGO receptor gene occur. Thus, this argument is inapposite. Second, Applicants are confused as to why one would have been motivated to make modifications to determine overall RNAi activity, if RNAi activity was not a motivation or factor in making the compounds, in the first place. Predictability as discussed *supra*, must also include an assessment of whether the compound will work for its intended purpose. The compounds in Elbashir that were 'more extensively' modified in one or both strands did not work for their intended purpose to mediate RNAi, thus Elbashir teaches

away from more extensive modification beyond 3'-terminal deoxy substitution when making compounds for the purpose of modulating RNAi.

Furthermore, the Office's statements that one "would be motivated to incorporate chemical modifications to about 50% to 100% . . . of the nucleotide positions to test the overall effect on RNAi activity as taught by Elbashir *et al.*" and that "there would be reasonable expectation of success to apply each of the claimed modifications to the chemically modified nucleic acid molecules of the claimed invention" are conclusory and lack evidentiary support. As discussed *supra*, the evidence clearly showed that more extensive modification of one or both strands abolished activity and that modifications in general yielded unpredictable results. *See* Parish and Elbashir. Likewise, other publications at the time uniformly suggest that skilled artisans followed the teachings of Elbashir, and designed siRNAs without any modifications other than the 2-deoxythymidine nucleotides at the 3'-end of the siRNA. *See, e.g.,* Bitko *et al.*, 2001, BMC Microbiology, 1 (34), page 9, left column, "Materials and Methods;" Kuman *et al.,* 2002, Malarial Journal, 1(5), page 9, right column, "Transfection by Inhibitory dsRNA;" and Holen *et al.,* 2002, Nucleic Acid Research, 30, pages 1757-66, Figures 1, 2, and 6.

These references contradict the Office's assertion that one would have been motivated to make the claimed modifications. Applicants respectfully request that the Office produce evidence that incorporation of 50-100 percent chemical modifications on <u>each</u> strand of a double stranded nucleic acid and having one or more 2'-O-methyl purines and one or more 2'-deoxy-2'-fluoro pyrimidines or alternatively, having at least two modifications that are different from each other, wherein one of the modification is 2'-O-methyl, to modulate expression of the NOGO receptor gene was within the common knowledge or routine at the time of Applicants' invention, or if based on personal knowledge, provide an affidavit or declaration setting forth specific factual statements and explanation to support the finding. "When a rejection in an application is based on facts within the personal knowledge of an employee of the Office, the data shall be as specific as possible, and the reference must be supported, when called for by the applicant, by the affidavit of such employee, and such affidavit shall be subject to contradiction or explanation by the affidavits of the applicant and other persons." (See MPEP 2144.03 and 37 CFR 1.104(D)(2)).

Finally, the Office asserts that one would have substituted the antisense of Groutsi with the modified double stranded nucleic acids of the invention as they are functional equivalents and "that substitution of one known element for another would have yielded predictable results at the time of the invention." To support its position, the Office cites to MPEP 2144.06 and a post-filing reference, Scanlon KJ (Current Pharmaceutical Biotechnology, 2004 Vol. 5:415-420.) Office Action at 23 and 24. The Applicants note that as Scanlon is a post-filing reference as acknowledged by the Office, it is not relevant under MPEP 2144.06. According to the MPEP 2144.06,"[i]n order to rely on equivalence, as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art." As discussed *supra*, a single stranded unmodified antisense RNA to NOGO and a double stranded nucleic acid with the presently claimed limitations, e.g., separate sense and antisense strands, 50-100% modification of each strand, differential purine and pyrimidine modification etc., are not equivalent. As the Office has failed to cite any prior art showing that they are equivalent, the Office has therefore not put forth a *prima facie* case of obviousness.

For all the reasons stated herein the cited references do not render the instant claims *prima facie* obvious. Accordingly, Applicant respectfully requests withdrawal of the 35 U.S.C. § 103(a) rejection.

## CONCLUSION

In view of the foregoing remarks, Applicants submit that the claims are in condition for allowance, which is respectfully solicited. If the Examiner believes a teleconference would expedite prosecution, she is urged to contact the undersigned before taking further action.

Respectfully submitted,

Date: March 18, 2008

/Anita J. Terpstra/

Anita J. Terpstra, Ph.D
Registration No. 47,132

**McDonnell Boehnen Hulbert & Berghoff LLP**
300 South Wacker Drive
Chicago, IL 60606

Telephone:312-913-0001
Facsimile: 312-913-0002